(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17486 A2

(51) International Patent Classification[7]: A61K 7/00

(21) International Application Number: PCT/IB00/01281

(22) International Filing Date:
8 September 2000 (08.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A001898 9 September 1999 (09.09.1999) IT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/17486 A2

(54) Title: METHOD FOR THE COSMETIC INTENSIVE TREATMENT OF SKIN IMPAIRMENTS AND BALDNESS BY APPLYING DEANOL OR DERIVATIVES THEREOF

(57) Abstract: The present invention relates to a method for the cosmetic treatment of impaired skin conditions, namely wrinkles, dermal striae and alopecia, which comprises selectively delivering deanol or a derivative thereof in a localized skin area affected by senescent fibroblasts, specific techniques to deliver deanol to senescent skin, new compositions comprising deanol i.a. a synergistic composition comprising deanol and vanadium salts and new esters of deanol.

METHOD FOR THE COSMETIC INTENSIVE TREATMENT OF SKIN IMPAIRMENTS AND BALDNESS BY APPLYING DEANOL OR DERIVATIVES THEREOF.

FIELD OF THE INVENTION

The present invention relates to a method for the cosmetic intensive treatment of skin impairments and baldness which comprises the stimulation of particular fibroblasts by applying deanol (N,N-dimethylethanolamine) or derivatives thereof.

More particularly, the invention relates to the cosmetic treatment of senescent impaired skin namely wrinkles, dermal striae and alopecia, through a particular technique providing selective stimulation of senescent fibroblasts by localized application of deanol or derivatives thereof.

The invention also concerns new compositions comprising deanol i.a. a synergistic composition comprising deanol and vanadium salts and new esters of deanol.

BACKGROUND OF THE INVENTION

The natural progression of skin ageing produces a progressive epidermal and dermal atrophy, is also know as "intrinsic ageing", whose progression along the time results from the combination of exogenous factors and the genetically programmed senescence.

The photoageing from long-term exposure to sunlight and UV sources further accelerates the intrinsic ageing. In this frame, a variety of evidences, such as epidermal dysplasia with cytologic atypia, the diffused damages to the connective tissue (elastosis), the increases of glycosaminoglycans with loss of collagen, the decrease of the keratinocyte polarity, as well as the increase of dermal elastin-

staining material by collagen degeneration had been histologically and biochemically correlated with the age progression.

The main sign of ageing are thus visually appreciable by the modification on the skin appearance, whose slow degeneration starts at the 25th to 30th year of age, to sharply increases from the 50th – 60th years on. The formation of wrinkles is correlated with a progressive degradation of the dermal fibrous proteins, the connective biopolymers primary characterized by their elastic behaviour.

A further unaesthetism due to fibroblast senescence and inactivation is known as dermal striae, i.e. flat skin marks. Said condition takes the appearance of striae distensae, i.e. straight cutaneous marks classified as striae atrophicae, striae albicantes, striae rubrae, sometimes associated obesity followed by slimming, emaciation, rapid growth, e.g. during puberty or adolescence. The use of corticosteroids is another cause of the dermal striae, as illustrated by Wach Fet al., in Skin Pharmacol. Appl. Skin Physiol, 11(1):43-51 (1998), and this may properly explain the formation of striae during pregnancy (striae gravidarum), thus correlated to the endogenous increase of cortisol release.

Fibroblasts are the primary cells which are specialized in the synthesis and extravasation of the fibrous and elastic proteins, namely collagen, elastin and fibronectine. The former predominate among the dermal proteins, which are overall essential to the structural and cosmetic integrity of the skin. However, it is well known that the fibroblasts biosynthesis of fibrous proteins decreases significantly with age.

During the senescence phase, fibroblasts also exhibit a low proliferative potential, i.e. the duplicative capacity of the cells. By all meanings, a senescent

fibroblast holds distinctive genotypic and phenotypic features in comparison with a corresponding "normal and young" proliferative fibroblast.

Besides their low proliferative capacity, senescent fibroblasts display a limited responsiveness to growth factors. In that sense, an enhancement of the proliferative capacity has been achieved by the treatment with epidermal and platelet-derived growth factors, as well as with insulin, glucocorticoids, extracts of Centella asiatica, Filicium decipiens, gingsenosides or gibberellin hormone-like vegetal substances. However, these substances are active in preserving the young phenotype, whereas old fibroblast respond little, if at all, to the treatment even at high concentrations.

A particular condition related to premature fibroblast senescence is the one provoking a further unaestethism such as the loss of hair, commonly known as alopecia. The fibroblast stimulation activates the dermal sheath cells surrounding upper follicular epidermis, so that new hair matrix and papilla can regenerate from the rest of the follicle, and eventually a hair shaft grows again. Thus, dermal papilla cells and probably dermal sheath cells have the ability to induce new hair matrices and to form hair bulbs under preferred environmental conditions, such as those provoked by substances having mitogenic effect on fibroblasts.

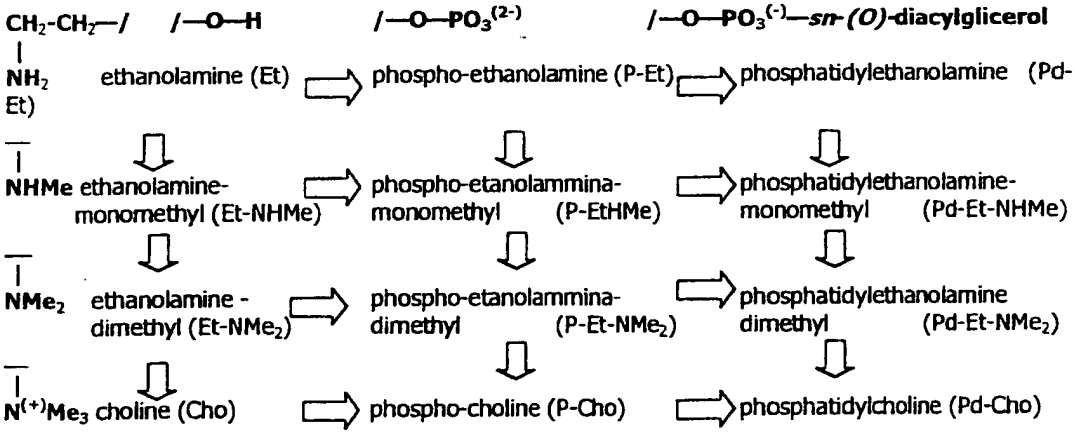
The new approach to the problem consists in the change of fibroblast membrane, i.e. altering the composition and signalling pattern through the change of the polar head of the cell membrane phospholipids.

Within cells, the key regulator of membrane functions is actually polyunsaturated phosphatidylcholine (PC), which is formed from choline and phosphoryl choline by the de novo synthesis. Lower methylated phosphatides, such as phosphatidyl N-monomethylethanolamine (PMME), phosphatidyl N-deanolamine

(PDME), and phosphatidylethanolamine (PE) may be increased by the supplementation of the lower methylated precursors (ethanolamine, methylethanolamine, deanolamine), as happens in cultured neuronal cells in the work of Dianous F and Kanfer J.N. in J. of Neurochem., 46, 6, 1859-1864 (1986).

The modification of phospholipid polar head groups is achieved by supplementation of the growth medium of cultured human fibroblasts with the ethanolamines and the phosphorylated ethanolamines at 80-200 μg/ml for 48 hr, as shown by Kanfer et al. in Biochem J., 264, 555-562, (1989). The methylation of the phospholipid precursors at different methylation level is carried out also in vivo models with formation of phosphorylated precursors and then the corresponding phospholipids. Therefore, the intermediate low methylated phospholipid and precursors can interconvert at any stage through phosphatidylethanolamine N-methyltransferase, as shown in the following scheme 1:

SCHEME 1



Therefore DMPE, naturally formed by phospholipase-D from deanolamine, may have a growth regulatory activity which is independent even from the role as phospholipid precursors.

The use of L-α-dipalmitoyl-phosphatidyl-N,N-dimethyl-ethanolamine (DPPDME; DPPE-NMe_2) to alter the membrane composition and activate the turn-over of senescent fibroblast by macrophages clean up and stimulation of the young proliferative fibroblasts is disclosed in EP-0533126. Nonetheless, the dosage level and bioavailability of this synthetic phospholipid has scarce effect on the unaestethic presence of wrinkles.

US 5554647 disclose that the topical application of deanol, optionally in combination with vegetal antioxidants substances and/or extracts having fibroblast stimulator activity, for the treatment of skin ageing.

It is known that vanadium compounds also modulates cell proliferation in a biphasic manner with similar potencies, as reported by Schieven GL et al. in J Trace Elem Med Biol, 270(35):110-5 (1997).

The use of solubilized vanadium salts in methods and compositions for treating both internal healing and alleviating dermal conditions such as skin wrinkles, reducing actinic keratoses, and healing damaged tissue is disclosed in WO9012563.

DESCRIPTION OF THE INVENTION

We have now surprisingly found out that despite its claimed anti-wrinkle activity, the conventional topical use of deanol reinforce the evidence of wrinkles, striae and other unaestethic effects due to ageing, as the composition topically administered on aged or impaired skin actually increases proliferation of the younger fibroblasts outside the wrinkles whilst the senescent fibroblasts in the inner part of the wrinkles are comparatively much less stimulated.

In fact, whereas the skin surrounding the wrinkle contains a greater amount of young fibroblasts, whilst in the wrinkly areas are predominantly found senescent fibroblasts. As pointed out hereinabove, young fibroblasts display a much higher

responsiveness to stimulation than senescent ones and, as a consequence, an indiscriminate application of a fibroblast stimulator agent produces a swelling effect which is strongly marked around the wrinkles, but much more slight inside the wrinkle.

Such an indiscriminate application therefore paradoxically increases the depth of the wrinkle by swelling the skin all around the wrinkle border but not producing a great effect in the portion of the skin affected by the ageing process and, for this reason, carrying principally senescent fibroblasts.

One of the purpose of the present invention is therefore to provide an effective method for selective treating impaired skin conditions, by administering deanol by using particular techniques.

The term "impaired skin conditions" designates in the present invention any condition pursuant to fibroblast degeneration, for example wrinkles, dermal striae and alopecia.

One of the aims of the present invention relates to a method for selective treating particular impaired skin conditions such as wrinkly skin and striae, by selectively applying deanol to the wrinkles and striae, thus avoiding the overall indiscriminate stimulation of fibroblasts and minimizing the activation of the younger ones.

Therefore, the present invention concerns a method for the cosmetic treatment of impaired skin conditions comprising selectively delivering deanol or a derivative thereof in a localized skin area affected by senescent fibroblasts.

The aim of the invention is achieved by provoking selective and exclusive stimulation of senescent fibroblasts by locally administering deanol or a derivative thereof directly on or inside the impaired or aged skin part.

More particularly, according to one of its aspects, the invention relates to a method for the cosmetic treatment of impaired skin conditions such as wrinkles, crow's feet, swellings, eyes rings and striae, which comprises locally administering an appropriate composition comprising deanol or a derivative thereof, either by intradermal or selective topical administration.

The expression "physiologically salt- or ester-derivative" designates in the present invention a derivative of deanol which is suitable for its topical or intradermal administration.

Preferred salt derivatives are deanol salts with an anion moiety of a mono-, di- or triprotic organic or inorganic acid.

Particularly advantageous salts are physiologically acceptable addition salts with an inorganic acid such as sulphuric, hydrochloric, phosphoric acid or with a organic acid such as pyruvic, acetic, benzoic, salicylic, succinic, nicotinic, maleic, methanesulphonic and lactic acid. Further suitable addition salts are those formed with amino acids, mono- di- and tricarboxylic acids, e.g. fatty acids.

Other preferred addition salts with deanol are those formed with an alpha hydroxy acid (AHA). The presence of an alpha hydroxy acid facilitates the increase in strength and firmness of dental and epidermal layers of the skin. The alpha hydroxy acid according to the present invention preferably has the following general structure:

$$R^2CHOHCOOR^1$$

wherein R^1 and R^2 are independently H, or C_1-C_{20} alkyl, arylalkyl or aryl, said alkyl group having a straight or branched chain or being a cycloalkyl and, in addition, R^2 optionally carrying one or more OH, CHO, COOH and C_1-C_9 alkoxy group. The

typical alkyl, aralkyl and aryl groups of R^1 and R^2 include for example methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl.

Preferred ester derivatives of deanol are esters with a glyceryl or phosphatidyl group, or an acyl moiety deriving from a mono- bi- tri-carboxylic acid of formula R-CO-, wherein R is a linear or branched, saturated or unsaturated C_1-C_{22} alkyl or C_1-C_{12} alkylaryl group, which is optionally carboxylated, carbonylated or hydroxylated.

Particularly preferred among ester derivatives are the fatty esters, more preferably saturated fatty acid esters, such those formed by acylation with lauric, myristic, stearic, oleoic acid, and the like. Further preferred ester are the emiesters formed with dicarboxylic acid, e.g. by the reaction of deanol with anhydrides such as succinic, sebacic, azelaic and the like.

Esters of deanol with fatty acids, namely with C_6-C_{22} mono- or di-carboxylic acids are new and represent a further object of the present invention.

According to a preferred embodiment, the invention concerns a method for the cosmetic treatment of aged skin which comprises locally administering an appropriate composition, either by intradermal or by localized topical administration on the affected portion of skin, said composition comprising deanol or a physiologically salt- or ester-derivative thereof.

Therefore, according to this particular embodiment, the present invention relates to a method for the treatment of impaired skin conditions such as wrinkles or other aged skin marks, which comprises intradermally injecting an effective amount of deanol, or an appropriate derivative thereof, exactly in internal part of the wrinkle, or of the particular other skin mark which has to be treated.

More particularly, for such an intradermal technique of administration, deanol or a suitable physiologically acceptable derivative thereof, is administered in the

form a suitable composition such as a sterile aqueous and hydroalcoholic solution or suspension, said composition optionally comprising coadjuvants, such as for example fibroblast stimulating agents and suitable conventional carriers.

The intradermal technique is carried out by syringe or dermojet and best performed with liquid formulations comprising deanol, preferably as an acid addition salt thereof.

In a preferred embodiment, the composition for the intradermal administration also comprises one or more amino-acids or oligopeptides.

No particular limitation is imposed on amino acids suitable for the present invention, and any neutral, basic and acidic amino acids can be used. Examples of such amino acids include glycine, alanine such as alpha-alanine, serine, cysteine, djenkolic acid, aminobutyric acid, threonine, valine, methionine, leucine, isoleucine, phenylalanine, tyrosine, thyroxine, proline, tryptophan, taurine, aspartic acid, glutamic acid, arginine, lysine, ornithine, and histidine, all of them being in any of the D, L or D,L forms or in mixture thereof.

The oligopeptides include, according to the present invention, natural origin and synthetic oligopeptides having a molecular weight of 3000 or less. Examples of the oligopeptides containing 2 to 10 amino acids are dipeptides, tripeptides, tetrapeptides, pentapeptides, up to decapeptides which are combinations of identical or different amino acids mentioned hereinabove.

The amino acids which are the constituents of these oligopeptides may be a single amino acid or any combinations of 2 or more amino acids. Illustrative examples include oligopeptides such as di L-arginine-L-aspartic acid, L-arginine-L-glutamine, glycylglycine, L-glutamic acid-D,L-alanine, di D,L-pyrrolidone carboxylic acid, L-alanyl-glycyl-glutamine, beta-alanyl-L-histidine, seryl-glycyl-

prolyne, L-leucyl-seryl-glycine, D,L-leucyl-glycyl-DL-phenylalanine and glutathione.

Particularly preferred amino-acids are glutamine, serine, lysine, proline and leucine, preferably in their L-form, which are advantageously administered at a 2-5% w/v concentration.

According to another preferred embodiment, the present invention relates to a method for the treatment of wrinkles and impaired skin, which comprises topically administering an effective amount of deanol, or an appropriate derivative thereof, on the particular localized portion of the impaired skin.

Such a topical local administration is suitably performed by a micro or a very small brush or a "dispensing pen", by carefully applying the composition comprising deanol or a derivative thereof, only the inner part of a wrinkle or on the stride pathway.

Appropriate compositions for the localized topical administration comprise for example gelled solutions, suspensions, and lotions, or ointment and emulsion wherein deanol or a derivative thereof, can optionally be present in combination with other fibroblast stimulating agents and optional suitable carriers, the proportion of the other fibroblast stimulating agents in the composition being up to 30% based on the total weight of the composition.

In a preferred form of this particular technique, deanol or a derivative thereof is selectively administered in the aged skin portion by a combination with an effective amount of one or more esfoliating agent.

Preferably, a suitable composition for the aforementioned administration comprises one or more esfoliating agent in a quantity comprised from 5% to 80%, more preferably from 10% to 70% by weight of the composition.

Preferred esfoliating agents are salicylic acid, trichloroacetic acid and alpha hydroxy acids (AHAs), which facilitate the opening of the stratum corneum and the structure of dermal tissue, thus improving the penetration and the activity of the active compound.

Preferred AHAs are low molecular weight monocarboxylic acids, in order to improve skin penetration and efficacy of the compositions by increasing percutaneous absorption, such as D,L-lactic acid, L-lactic, glycolic acid, mandelic acid, and mixtures thereof. The latter AHAs are also known for their ability to stimulate fibroblast metabolism and turn-over.

More particularly AHAs can be added to the compositions comprising deanol or a derivative thereof or alternatively, deanol can be directly salified by an appropriate AHA. According to a particularly advantageous embodiment, AHAs are present in the compositions for this particular administration and the amount of said AHAs is up to 70% based on the total weight of the composition.

In a further preferred embodiment of the present invention, the invention relates to compositions comprising deanol or a derivative thereof also comprising one or more coadjuvant compounds such as active compounds selected from the group consisting of fibroblast stimulators, antioxidants, collagenase inhibitors and anti-inflammatory agents.

Particularly preferred fibroblast stimulators are those contained in specific vegetal extracts, or glycosaminoglycanes, peptidic growth factor, insuline and insulino-mimetic substances, and mono- oligo-saccharides.

Illustrative examples of glycosaminoglycans include hyaluronic acid, heparin, heparan and chondroitin sulfate, polysulfated glycosaminoglycan, and keratan sulfate.

Illustrative examples of plant extracts include Aloe spp., Gymnena sylvestris, Centella asiatica, Panax ginseng, ivy, Fusarium monoliform, and Filicium decipiens.

Illustrative examples of peptidic growth factors are the fibroblast growth factors (FGF), the epidermal growth factors (EGF), the transforming growth factor-alpha (TGF)

Illustrative examples of mono- oligo-saccharides include glucose, fructose, galactose, lactose, trehalose, ribose, mannan, beta-glucans.

Particularly preferred antioxidants are ascorbates, tocopherols, retinoids and carotenoids.

Particularly preferred collagenase inhibitor is retinoic acid.

Particularly preferred anti-inflammatory agents include, but are not limited to, rosmarinic acid, glycyrrizinate derivatives, alpha bisabolol, azulene and derivatives thereof, asiaticoside, sericoside, ruscogenin, escin, escolin, quercetin, rutin, betulinic acid and derivatives thereof, catechin and derivatives thereof.

The compositions according to the invention may also comprise any cosmetically acceptable ingredients. The expression "cosmetically acceptable ingredients" designate in the present specification products which are suitable for their use in cosmetic treatments, for example those included in the INCI list drawn by the European Cosmetic Toiletry and Perfumery Association (COLIPA) and issued in 96/335/EC "Annex to Commission Decision of 8 May 1996" and further modifications.

According to another preferred embodiment, the present invention relates to a method for the treatment of striae, which comprises topically administering on the particular localized portion of the skin affected by the striae, an appropriate cover releasing an effective amount of deanol or an appropriate derivative thereof.

This specific technique is made possible because striae are frequently large enough to allow the use of localized covers which need to be cut in the same shape of the area to be treated. Examples of such covers are patches, plasters, bandages, dressings, gauze pads and the like, which are, according to the invention, soaked by an appropriate amount of deanol or a derivative thereof.

More particularly, for this specific administration route, deanol one of its derivatives, is administered in suitable compositions optionally in combination with other fibroblast stimulating agents and/or esfoliating agent.

In the light of the above, it is clear to the skill in the art that different techniques can be performed in order to locally administer deanol or a derivative thereof, all of them being carried out for stimulating exclusively senescent fibroblasts in the impaired skin marks. Other techniques can be possibly performed according to the invention, bearing in mind that it is important to selectively treat only said senescent fibroblasts in order to achieve the desired cosmetic result.

The content of deanol as the cosmetic active principle in the above compositions varies according to the administration route and the degree of the impairment of the skin. In general, the proportion of deanol is comprised between 0.1 and 50% by weight, and preferably between 1 and 20% by weight, advantageously between 1 and 10% by weight, based on the total weight of the composition.

According to the method of the invention, said compositions are preferably administered by a professional cosmetologist or beautician or aesthetic dermatologist by injection on the wrinkles and striae, or by application with a thin brush or a bendage, the latter could be as well performed by the same subject affected by the aesthetic impairment.

We have also surprisingly found that vanadium compounds in the (IV) and (V) oxidation status have a high synergistic behaviour in potentiating the fibroblast stimulation exerted by deanol and that vanadium (IV) and (V) compounds greatly enhance the efficacy of deanol the cosmetic intensive treatment of skin impairments and alopecia, namely baldness.

Therefore, according to another of its aspects, the present invention relates to a synergistic combination of deanol or a derivative thereof and one or more vanadium compounds for the treatment of skin impairments and baldness.

According to a further aspect, the present invention relates to a synergistic cosmetic composition comprising deanol or a derivative thereof and one or more vanadium compounds.

Said cosmetic composition preferably comprise vanadium (IV) or (V) compounds at a proportion in the range of 10^{-10} to 10^{-3} moles/kg, preferably at 10^{-7} to 10^{-5} mmoles/g.

Illustrative examples of suitable vanadium (V) compounds useful in the practice of the present invention include sodium metavanadate ($NaVO_3$), orthovanadate (Na_3VO_4) and pyrovanadate ($Na_4V_2O_7$), corresponding salts with potassium (KVO_4), ammonium (NH_4VO_3), calcium ($Ca_3(VO_4)_2$), iron ($Fe(VO_3)_3$), and corresponding salts of vanadates with magnesium, zinc, aluminum, and the like; the vanadium (V) oxides such as the pentoxide (V_2O_5), oxytrichloride ($VOCl_3$), oxytribromide ($VOBr_3$) and the like, as well as polymers such as a dimer ($H_2V_2O_7$), a trimer (V_3O_9), a decamer ($HV_{10}O_{28}$), and the like.

Illustrative examples of suitable vanadium (IV) compounds useful in the practice of the present invention include vanadyl sulfate ($VOSO_4$), and corresponding compounds with acetate, etc; vanadium (IV) oxyhalides such as the

oxychloride ($VOCl_2$), oxydibromide ($VOBr_2$), and oxydifluoride (VOF_2); vanadium (IV) halides such as the tetrachloride (VCl_4), tetrabromide (VBr_4) and tetrafluoride (VF_4) and the like; vanadium dioxide (VO_2) and vanadium tetraoxide (V_2O_4).

Furthermore, the vanadium (IV) or (V) compounds may be present in form of chelates, clathrates or other complexes, including those with amino acids, proteins, peptidic growth factors, nucleic acids, phosphates, phospholipids, fatty acids, prostaglandins, AHAs, retinoids, tris-edatate, glycols, catechols, glutathione, and the like.

The vanadium (IV) or (V) compounds may also be present as salts of organic acids and vanadium contained in tunicates (sea squirts), some mushroom species and plants, and other organic sources. Specific examples of vanadium organometallic compounds include vanadyl salts of organic acids such as: vanadyl linoleate, oleate, palmitate, phenolate, resinate and stearate.

Said synergistic compositions are suitable for the treatment of impaired skin conditions according to the method and the preferred embodiments of the invention hereinabove, and for the topical treatment of skin relaxation, such as breast skin relaxation, as well as for the treatment of alopecia.

According to another of its aspects, the invention relates to a method for the treatment of impaired skin conditions provoking alopecia, which comprises topically administering to a subject's scalp an effective amount of a combination of at least a vanadium derivative and deanol or a derivative thereof.

The combination of at least a vanadium derivative and deanol or a derivative thereof, used in the method of the present invention, are applied in the form of appropriate compositions, namely in the form of the compositions usually employed for the administration of active ingredients on human scalp.

Therefore, the invention also relates to a method for treating alopecia which comprises administering to the affected area a cosmetic composition comprising at least a vanadium derivative and deanol or a derivative thereof as the active ingredients.

Said compositions may take a wide variety of forms such as, for example, solid forms, e.g. powders; liquid forms, e.g. solutions or suspensions in aqueous or oily mediums; semi-liquid formulations, e.g. creams, gellies, pastes, ointments, salves.

Other such compositions are preparations of the cosmetic type, such as toilet waters, packs, lotions, skin milks or milky lotions.

Thus, said preparations may contain, besides the active ingredient, components usually employed in such preparations, examples of such components being oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes, dyestuffs, lower alkanols. If desired, further ingredients may be incorporated in the compositions, e.g. anti-inflammatory agents, antibacterials, antifungals, disinfectants, vitamins, sunscreens, anti-acne agents, antibiotics, etc.

Examples of oils comprise fats and oils such as olive oil, and hydrogenated oils; waxes such as beeswax and lanolin; hydrocarbons such as liquid paraffin, ceresin, and squalane; fatty acids such as stearic acid and oleic acid; alcohols such as cetyl alcohol, stearyl alcohol, lanolin alcohol, and hexadecanol; and esters such as isopropyl myristate, isopropyl palmitate and butyl stearate. Further examples of oils are those containing essential fatty acids (EFAs), such as alpha-linoleic acid, gamma-linolenic acid, homo-gamma-linolenic acid, columbinic acid, eicosa-(n-6,9, 13)-trienoic acid, EPA, DHA, gamma-linolenic acid, timnodonic acid, hexaenoic acid.

As examples of surfactants there may be cited anionic surfactants such as sodium stearate, sodium cetylsulfate, polyoxyethylene laurylether phosphate, sodium N-acyl glutamate; cationic surfactants such as stearyldimethylbenzylammonium chloride and stearyltrimethylammonium chloride; ampholytic surfactants such as alkylaminoethylglycine hydrochloride solutions and lecithin; and nonionic surfactants such as glycerin monostearate, sorbitan monostearate, sucrose fatty acid esters, propylene glycol monostearate, polyoxyethylene oleylether, polyethylene glycol monostearate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene coconut fatty acid monoethanolamide, polyoxyethylene polyoxypropylene glycol, polyoxyethylene castor oil, and polyoxyethylene lanolin.

Examples of humectants include glycerol, 1,3-butylene glycol, and propylene glycol; examples of lower alcohols include ethanol and isopropanol; examples of thickening agents include xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol and sodium carboxymethyl cellulose; examples of antioxidants comprise butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate and citric acid ethoxyquin; examples of chelating agents include disodium edetate and ethanehydroxy diphosphate; examples of buffers comprise citric acid, sodium citrate, boric acid, borax, and disodium hydrogen phosphate; and examples of preservatives are methyl parahydroxybenzoate, ethyl parahydroxybenzoate, dehydroacetic acid, salicylic acid and benzoic acid.

For preparing ointments, creams, lotions, milks, and the like, typically from 0.1 to 30% in particular from 1 to 5% of deanol or a derivative thereof and from 10^{-3} to 10^{-10} moles/kg, in particular from 10^{-5} to 10^{-7} moles/kg of a vanadium derivative.

In ointments or creams, the carrier is present for example in a proportion of 1 to 20%, in particular 5 to 15% of a humectant, 0.1 to 10% in particular from 0.5 to

5% of a thickener and water, or said carrier may consist of 70 to 99%, in particular 20 to 95% of a surfactant, and 0 to 20%, in particular 2.5 to 15% of a fat; or 80 to 99.9% in particular 90 to 99% of a thickener; or 5 to 15% of a surfactant, 2-15% of a humectant, 0 to 80% of an oil, very small (<2%) amounts of preservative, colouring agent and/or perfume, and water. In a lotion, the carrier for example consists of 2 to 10% of a lower alcohol, 0.1 to 10% or in particular 0.5 to 1% of a surfactant, 1 to 20%, in particular 3 to 7% of a humectant, 0 to 5% of a buffer, water and small amounts (<2%) of preservative, dyestuff and/or perfume. In a milk, the carrier typically consists of 10-50% of oil, 1 to 10% of surfactant, 50-80% of water and 0 to 3% of preservative and/or perfume. In the afore-mentioned preparations, any % refers to a % by weight.

The humectant, surfactant, oil, etc. referred to in said preparations may be any such component used in the cosmetic arts but preferably will be one or more of the aforementioned components. Further, when in the above compositions one or more of the components make up the major part of the composition, the other ingredients can evidently be not present at their indicated maximum concentration and therefore will make up the remainder of the composition.

In a preferred embodiment, the present invention relates to a composition for the treatment of baldness comprising deanol or a derivative thereof combined with a vanadium compound which also comprises one or more trichogenic agents.

Illustrative examples of trichogenic agents are minoxidil, 2,4-diamino-pyrimidine 3-oxide, odd numbered fatty acids (e.g. n-hendecanoic, n-tridecanoic, n-pentadecanoic, n-heptadecanoic acids), pyroglutamic acid and esters thereof, plant extracts and derivatives with estrogen-like activities and/or vasokinetic activity

(capillary stimulation), such as visnadine, kellin, esculoside, esculetin, xymenynic acid, raubasine and vincamine.

The compositions comprising deanol or a derivative thereof and one or more vanadium compounds may also comprise one or more active compounds selected from the group consisting of fibroblast stimulators, antioxidants, collagenase inhibitors and anti-inflammatory agents, herein above described.

The compositions of the present invention are preferably administered one to 3 times per day on the area affected by alopecia for a period of time varying from few days to 6-8 months, advantageously until the desired hair growth effect is obtained, in a quantity sufficient to deliver on the scalp at least from about 0.1 to 1 g of deanol.

The following examples are preferred features of the invention but are not intended to limit it in any way.

EXAMPLES

Preparative Example 1 – Deanol biadipate

In a round bottom flask (0.5 l) equipped with a magnetic stirrer and a dropping-funnel, 73 g of adipic acid (0.5 moles) were poured in 100 ml of water, then heated to 80-90°C and stirred until solubilization. A mixture of 44.5 g of deanol (0.5 moles) and 50 ml of water is then added dropwise, the resulting solution is cooled to 4°C and then kept at standing at this temperature for 6 hours until complete precipitation. The precipitate is filtered, washed with icy water and dried under vacuum at mild temperature, providing 77.5 g (yield 66%) of white acicular product.

Preparative Example 2 – Solution of deanol D,L-lactate with VO-lactate $7x10^{-3}$ M

56.25 g of D,L-lactic acid 80% in water (0.5 M) were mixed with 22.165 g (25 ml) deanol (0.5 M) in 59 ml of water. Then 0.72 g of $VOSO_4$ 65% are added and solubilized under slow stirring.

Preparative Example 3 – Solution of deanol pyruvate 10%

24.5 g of pyruvic acid (0.25 M) were solubilized with 22.165 g (25 ml) of deanol (0.25 M) in 450 ml of water.

Preparative Example 4 – Solution of deanol azelate 15%

32 g of azelaic acid (0.25 M) were solubilized in 365 ml of water with 22.165 g (25 ml) of deanol (0.25 M) in 365 ml of water.

Preparative Example 5 – Deanol O-laurate

In a round bottom flask (0.5 l) equipped with a magnetic stirrer and a reflux condenser, 5.48 g of lauroyl chloride (0.25 moles) are poured in 200 ml of dichlorohexane and a solution of 3.1 g (3.5 ml) g of deanol (0.35 moles) in 50 ml of dichlorohexane are then additioned dropwise under stirring. The reaction mixture is heated to reflux for 1 hours, then allowed to cool under stirring.

The deanol O-laurate formed during the reaction does precipitate from the solution as hydrochloride, is thus filtered and the filtrate washed with dichlorohexane, and dried to provide a white powder. The powder is then poured in a 500 ml separatory funnel along with 50 ml chloroform and 3x50 ml of sodium bicarbonate, then with distilled water until neutral pH. Finally the organic phase was dried, and evaporated under reduced pressure, to provide 22.5 g (yield 34 %) of a whitish waxy powder.

Preparative Example 6 - Deanol O-emisuccinate

50 g of succinic anhydride (0.5 moles) are solubilized in 250 ml of chloroform, under stirring, then a solution of 44.5 g of deanol (0.05 mole) in 50 ml of chloroform is added dropwise, and the reaction mixture is stirred and heated to reflux for 3 hours. After cooling to room temperature, the reaction mixture is added with 100 ml of sodium bicarbonate, the aqueous phase is discharged and the phase oily phase is washed with water, dried and evaporated, to provide 41 g (yield 40 %) of a waxy powder.

Example 1 – Microinjection of deanol lactate plus vanadium(IV) in wrinkles

One female subject ageing 48 years was treated with an esthetic cream containing lidocaine (AMLA®), thereby applied to the skin to reduce the pain in view of the subsequent injection.

The subject is set in an upright position to evaluate the extent and position of wrinkles and folds in the skin, and her face was cleaned with a soapfree cleanser and rinsed with water. Then the areas to be treated were wiped with alcohol and patted dry. After 45 minutes, the lidocaine was removed and the skin is again wiped with alcohol.

With a fine-gauge needle, the solution from the Preparative Example 2 was diluted to 25% with sterile water and injected into the wrinkle lines. Occasionally, the subject was asked to move the forehead, scowl, squint or otherwise exaggerate the facial expression to emphasize the wrinkles lines which much needed to be corrected. For forehead lines, the deanol was injected in a horizontal fashion inject, with small amounts of deanol applied into the dermis across the area treated.

The subject was monitored after 1 month, with a visible attenuation of the facial wrinkles, which were partially attenuated. After 2 months the treatment was

repeated, and the follow-up after one month later indicate that the wrinkled areas were smoothed, particularly the previous expression mark on the forehead and the ring around the eyes were significantly less pronounced.

Example 2 – Microinjection of deanol pyruvate in wrinkles

The same procedure of Example 1 was applied to a female subject ageing 53 with visible evidences of the combination of intrinsic ageing with photoageing, but instead of the solution from the Preparative Example 2 was administered a sterile composition containing the following ingredients:

deanol pyruvate from the Preparative Example 3	5.0 g
alpha-tocopherol	0.2 g
Centella asiatica extract	1.3 g
ethyl alcohol	7.0 g
distilled water	qb to 100 g

The injection areas exhibited a visible redness, which disappeared after 3 to 5 days. The treatment was repeated after 1 month, and the subject control by the next month shown a significant improvement of the aesthetic condition of wrinkles, whose deepness and appearance were significantly attenuated.

Example 3 and Comparative Example 1 – Application of deanol in wrinkles: localized vs diffused local application

Two gels was prepared by a high-speed mixer the following ingredients:

	gel of Example 3	gel of Comparative Example 1
deanol	5.0 g	5.0 g
glycolic acid	20.0 g	8.0 g
alpha-tocopherol	0.5 g	0.5 g
retinoic acid	0.2 g	0.2 g

xanthan gum	1.2 g	1.2 g
deionized water	qb to 100 g	qb to 100 g

A female subject ageing 43 was treated by a professional beautician with the gel of Example 3, thereby applied with a thin brush on the wrinkles inner part of the right side of the face. The counterpart was treated with a diffused application on skin of the gel of Comparative Example 1. After 30 minutes both facial sides were rinsed with water and padded.

The subject was instructed to continue the treatment at home by separately applying the aforementioned methods on the two sides. After 45 days the subject was visually evaluated. The wrinkles of the right side were smoother and less pronounced, whereas the counterpart showed an overall increase of the skin consistency and bulk, except that the wrinkle lines appear more marked and clearly delineated on the skin background.

Example 4 – Transdermal patch with deanol biadipate for skin striae

Deanol biadipate from the Preparative Example 1 is incorporated in the adhesive mass in controlled release patches with the following compositon:

deanol biadipate of the Preparative Example 1	10.0 g
lactose	38.8 g
saturated triglycerides	2.2 g
polyisobuthene	22 g
hydrogenated colofonia	19.5 g
polyalkadiene	19.5 g

The transdermal patch is made of vertical strips (60 cm), each composed of three layers, i.e. a basal sheet, an adhesive film containing the active ingredients, and a coverage film.

The patch were customarily cut in strips to match the geometrical feature of thigh striae gravidarum of a 32 years old post-pregnant female subject, and applied thereof during the first session. The active ingredient is released during 24 hours, thus ensuring a continuous administration. The subject was given a number of strips of the same size and shape and instructed to substitute the former strips every day at the morning for 40 days, and wear each strips until next day. After this period the subject's thigh shown a marked improvement of the aesthetic condition, with a decrease of hard touch and an increment of volume in the striae area, which appears significantly less evident.

Example 5 – Microinjection of deanol O-succinate in striae

Deanol O-succinate from the Preparative Example 6 was mixed in a sterile solution containing:

deanol O-succinate from the Preparative Example 6	2.5 g
alpha-tocopherol	0.5 g
glycolic acid	3 g
L-serine	1.05 g
L-proline	1.15 g
L-glutamine	1.46 g
L-lysine	1.46 g
L-leucine	1.31 g
distilled water	qb to 100 g

A female subject ageing 27 years with a history of juvenile obesity followed by a fast weight loss at 19 years of age showing striae albicantes on the region below the breast was submitted to injection with the aforementioned composition. The treatment was carried out on the border of the affected area and in the lower part of

the breast, then repeated after one month. At the first monitoring performed by the next month, the appearance of rubescence within the striae was noticeable. The next check a month later showed a reactivation of the treated area with a transition to the "striae rubrae", thus characterized by a pink-purple color of the skin. The last check after the following month revealed a marked improvement of the condition, with the formerly affected area scarcely visible. The subject's breasts had also a acquired more volume and consistency.

Tricologic Examples 1,2,3 – Lotions for hair

100 g of each hydroalcoholic lotions contain:

Lotion of Tricologic	Example 1	Example 2	Example 3
deanol lactate of Preparative Example 4	3.7 g	-	-
deanol O-laurate of Preparative Example 5	-	5.0 g	4.0 g
minoxidil	-	-	1.5 g
tocopheryl acetate	0.15 g	0.15 g	0.15 g
vanadil sulfate	0.01 g	-	-
glycolic acid	3.0 g	-	-
lauric acid	0.3 g	0.3 g	0.3 g
perfume	0.3 g	0.3 g	0.3 g
BHT	0.01 g	0.01 g	0.01 g
ethyl alcohol 40° v/v qb	to 100 g	to 100 g	to 100 g

The hydroalcoholic solutions were packed in 20 ml jars and sealed.

3 subjects aged between 26 and 39 with a history of male pattern alopecia were given each a different composition. Subject #1, #2 and #3 were thereby

instructed to apply in the scalp area once-a-day (preferably at night, before resting) from about 3 to 5 ml of the lotions of Trichologic Example 1, 2 and 3, respectively.

At the first check after 1 months of treatment on the area of baldness, no evidence of changes were observable. However, by the 2nd month there were a definite increase evidence of increased hair growth in all subject. Particularly, at this time the hairs of subject #1 and #3 were both larger and coarser then before the treatment; whilst in subject #2 the improvement was not evident, although the microscopy analysis revealed that the treatment had activated vellus hairs to become terminal hairs.

After 3 months of treatment the effect was observable in all subjects, with evidences to actually reverse the male pattern alopecia.

In summary, the topical use of a synergistic composition comprising a vanadium derivative and deanol or derivatives thereof definitely stimulate hair growth when applied to the human scalp where it is effective in preventing and/or reversing male pattern alopecia. Noteworthy, best results are obtained by daily occluding topical application for a period of time sufficient to effect hair growth.

CLAIMS

1. A method for the cosmetic treatment of impaired skin conditions which comprises selectively delivering deanol or a derivative thereof in a localized skin area affected by senescent fibroblasts.
2. Method according to Claim 1, for the cosmetic treatment of wrinkles, crow's feet, swellings, eyes rings and striae, which comprises locally administering an appropriate composition comprising deanol or a physiologically acceptable addition salt- or ester-derivative thereof, either by intradermal or by selective topical administration.
3. Method according to Claim 2, wherein the physiologically acceptable addition salt is selected in the group consisting in a salt with sulphuric, hydrochloric, phosphoric, azelaic, succinic, adipic, pyruvic, acetic, benzoic, salicylic, nicotinic, maleic, methanesulphonic, amino acids and fatty acids.
4. Method according to Claim 2, wherein the physiologically acceptable salt is a salt with an alpha hydroxy acid.
5. Method according to Claim 4, wherein the alpha hydroxy acid has the formula

$$R^2CHOHCOOR^1$$

wherein R^1 and R^2 are independently H, or C_1-C_{20} alkyl, arylalkyl or aryl, wherein said alkyl group having a straight or branched chain or being a cycloalkyl and, in addition, R^2 optionally carrying one or more OH, CHO, COOH and C_1-C_9 alkoxy group.

6. Method according to Claim 2, wherein physiologically acceptable esters are selected in the group consisting in esters with a glyceryl group, a phosphatidyl group and an acyl moiety of a mono- bi- tri-carboxilic acid of formula R-CO,

wherein R is a linear or branched, saturated or unsaturated C_1-C_{22} alkyl or C_1-C_{12} alkylaryl group optionally being carboxylated, carbonylated or hydroxylated.

7. Method according to any one of the preceding Claims which comprises administering a composition comprising as the active principle 0.5 to 50% by weight of deanol.
8. Method according to any of the preceding Claims, which comprises intradermically injecting exactly in the internal part of the wrinkle or of the particular other skin marks which has to be treated, an effective amount of deanol, or an appropriate derivative thereof, in the form of a suitable sterile liquid composition.
9. Cosmetic composition for performing the method of Claim 8, further comprising one or more aminoacid or oligopeptide.
10. Cosmetic composition according to Claim 9 wherein the aminoacid is selected in the group consisting in L-serine, L-proline, L-glutamine, L-lysine, and L-leucine.
11. Method according to Claims 1 to 7, which comprises topically administering by a micro or a very small brush, an effective amount of deanol, or an appropriate derivative thereof, on the particular localized portion of the impaired skin
12. Method according to Claims 1 to 7, which comprises topically administering on the particular localized portion of the impaired skin affected by striae, an appropriate patch releasing an effective amount of deanol or an appropriate derivative thereof.
13. Cosmetic composition for performing the methods of Claims 11 and 12, further comprising one or more esfoliating agents.

14. Cosmetic composition according to Claim 13 wherein the esfoliating agent is an AHA.
15. Cosmetic composition according to Claim 14 wherein the AHA is selected in the group consisting in glycolic acid, lactic acid, mandelic acid and mixture thereof.
16. Cosmetic composition comprising deanol or a derivative thereof and at least a vanadium compound.
17. Cosmetic composition according to claim 16 which comprises 10^{-10} to 10^{-3} mmoles/g of a vanadium (IV) or (V).
18. A method for the treatment of alopecia which comprises topically administering to a subject's scalp an effective amount of the composition of Claim 16 or 17.
19. Cosmetic composition for performing the method of Claim 18 further comprising one or more additional trichogenic agents.
20. Cosmetic composition according to Claim 18 or 19 wherein the additional trichogenic agent is selected in the group consisting in minoxidil, 2,4-diamino-pyrimidine 3-oxide, odd numbered fatty acids, pyroglutamic acid and esters thereof.
21. Cosmetic composition according to Claim 18 or 19 wherein the additional trichogenic agent is a plant extracts and derivatives with estrogen-like activities and/or vasokinetic activity selected in the group consisting in visnadine, kellin, esculoside, esculetin, xymenynic acid, raubasine, vincamine, or mixture thereof.
22. Cosmetic composition for performing the method of Claims 8 or 18, further comprising one or more fibroblast stimulators.
23. Cosmetic composition according to Claim 22 wherein the fibroblast stimulator is a glycosaminoglycan selected in the group consisting in hyaluronic acid, heparin,

heparan and chondroitin sulfate, polysulfated glycosaminoglycan, and keratan sulfate.

24. Cosmetic composition according to Claim 22 wherein the fibroblast stimulator is a plant extracts selected in the group consisting in Aloe spp., Gymnena sylvestris, Centella asiatica, Panax ginseng, ivy, Fusarium monoliform, and Filicium decipiens.

25. Cosmetic composition according to Claim 22 wherein the fibroblast stimulator is a peptidic growth factors selected in the group consisting in fibroblast growth factors (FGF), epidermal growth factors (EGF), and transforming growth factor-alpha (TGF).

26. Esters of deanol with (C_6-C_{22})-mono- or di-carboxylic fatty acids.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) Internati nal Publication Number
WO 01/17486 A3

(51) International Patent Classification[7]: A61K 7/48, 7/06, C07C 219/08, 219/06

(21) International Application Number: PCT/IB00/01281

(22) International Filing Date:
8 September 2000 (08.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A001898 9 September 1999 (09.09.1999) IT

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(72) Inventor: GHISALBERTI, Carlo [BR/BR]; Rua Luis Dias, 85/61, Itaim-Bibi, CEP-04542-080 São Paulo, SP (BR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

(88) Date of publication of the international search report:
10 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/17486 A3

(54) Title: DEANOL OR DERIVATIVES FOR THE TREATMENT OF SKIN IMPAIREMENTS AND BALDNESS

(57) Abstract: The present invention relates to a method for the cosmetic treatment of impaired skin conditions, namely wrinkles, dermal striae and alopecia, which comprises selectively delivering deanol or a derivative thereof in a localized skin area affected by senescent fibroblasts, specific techniques to deliver deanol to senescent skin, new compositions comprising deanol i.a. a synergistic composition comprising deanol and vanadium salts and new esters of deanol.

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/IB 00/01281

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/06 C07C219/08 C07C219/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2001	01/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, J.P.

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/IB 00/01281

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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